REMARKS

Summary of the Office Action

Claims 1-41, 46-53, 58-70, and 73-75 are pending in the application. Claims 22-41, 49-53, and 70 are withdrawn from consideration. Claims 1-21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of co-pending U.S. Serial No. 10/947,455, and over claims 1-24, 51-54, 66-80, and 82-85 of co-pending U.S. Serial No. 10/777,517. Claims 1-9, 11, 12, 15, 20, 21, 46-48, 58-63, 66, and 73-76 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Siegel et al. (U.S. Patent No. 6,204,245; hereafter "Siegel"). Claims 10 and 62 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Siegel in view of The Merck Index monograph numbers 04972 and 03712. Claims 13, 14, 16-18, 64, 65, and 67-69 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Siegel in view of Linden et al. (*Am. J. Med.* 107:595-605, 1999; hereafter "Linden"), Guenther (*J. Am. Acad. Dermatol.* 43:S36-S42, 2000), and Mitra (*Indian J. Dermatol. Venereol. Leprol.* 67:292-293, 2001). Lastly, claims 13, 14, 64, and 65 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Siegel in view of Ahmed (U.S. Patent No. 6,281,248) and The Merck Manual Section 4, Chapter 44, Asthma.

Claim Amendments

Claims 1, 58, 73, 74, and 76 have been amended. Claims 46-48, 59-65, 67-69, and 75 have been canceled. Claims 1, 73, and 74 have been amended to specify that the SSRI and the corticosteroid are present "in amounts that together are sufficient *in vivo* to mediate a synergistic decrease in proinflammatory cytokine secretion or production." Similarly, claims 58 and 76 have been amended to specify that the SSRI and the non-steroidal calcineurin inhibitor are "present in amounts that together are sufficient *in vivo* to mediate a synergistic decrease in proinflammatory cytokine secretion or production."

Support for the amendment of claims 1, 73, and 74 is found in previously pending claim 1 and in Tables 15-22 of the specification, and support for the amendment of claims 58 and 76 is found in Tables 25-30 of the specification. No new matter has been added by the present amendment. Applicants reserve the right to pursue any canceled subject matter in a continuation application.

Rejections Based on Double Patenting

Claims 1-21 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of co-pending U.S. Serial No. 10/947,455, and over claims 1-24, 51-54, 66-80, and 82-85 of co-pending U.S. Serial No. 10/777,517. These are provisional rejections, as the '455 and '517 applications have not yet issued as patents. Applicants wish to hold these rejections in abeyance until indications of allowable subject matter in this application have been received.

Rejections under 35 U.S.C. § 103(a)

Claims 1-18, 20, 21, 46-48, 58-69, and 73-76 stand rejected as being obvious over Siegel, either alone or in combination with one or more of The Merck Index monograph numbers 04972 and 03712, Linden, Guenther, Mitra, Ahmed, and The Merck Manual Section 4, Chapter 44. Claims 46-48, 59-65, 67-69, and 75 have been canceled and therefore, the rejections of these claims are moot. Applicants respectfully traverse the rejections of claims 1-18, 20, 21, 58, 66, 73, 74, and 76.

The Office cites Siegel as providing the basis for the combination of an SSRI and a corticosteroid. The Office cites the additional references for teaching additional elements of the pending claims (i.e., infliximab, etanercept, retinoids, vitamin D analogs, psoralens, and beta receptor agonists).

Applicants previously submitted in the Remarks filed on April 10, 2008, that the rejections under 35 U.S.C. § 103(a) should be withdrawn as the claimed invention is

directed to an unexpected, synergistic effect of the combination of an SSRI and a corticosteroid on proinflammatory cytokine secretion and production. In response, the Office stated that the pending claims did not read on the synergistic effect (Office Action, page 3). Applicants have amended the claims and submit that, as the claims now read on the unexpected synergistic effect that is not described in any of the cited prior art references, the obviousness rejections may now be withdrawn. Applicants' reasoning is discussed in greater detail below.

The Pending Claims are Directed to Unexpected, Synergistic Effects

Claims 1, 58, 73, 74, and 76 have been amended to specify the unexpected, synergistic effects observed for the combination of an SSRI and a corticosteroid, and the combination of an SSRI and a non-steroidal calcineurin inhibitor on decreasing proinflammatory cytokine secretion/production.

The specification provides data that demonstrate the unexpected effect of the combination of an SSRI and a corticosteroid (see, Tables 15-22), and the combination of an SSRI and a non-steroidal calcineurin inhibitor (see, Tables 25-30) on decreasing proinflammatory cytokine secretion and production. In particular, the specification provides data showing that several combinations of an SSRI and a corticosteroid mediate a synergistic decrease in TNFα secretion: paroxetine and prednisolone (Table 15, page 84; 0.375 μM paroxetine + 0.025 μM prednisolone); fluoxetine and prednisolone (Table 16, page 84; 7.23 μM fluoxetine + 0.006 μM prednisolone); fluoxetine and budesonide (Table 17, page 84; 0.009 μM fluoxetine + 0.009 μM budesonide); paroxetine and dexamethasone (Table 18, page 85; 3.0 μM paroxetine + 0.0063 μM dexamethasone); fluoxetine and dexamethasone (Table 19, page 85; 0.036 μM fluoxetine + 0.0024 μM dexamethasone); fluoxetine and prednisolone (Table 20, page 85; 1.80 μM fluoxetine + 0.0160 μM prednisolone); paroxetine and prednisolone (Table 21, page 86; 3.30 μM paroxetine + 0.016 μM prednisolone); and sertraline and prednisolone (Table 22, page 86;

4.0 μM sertraline + 0.0160 μM prednisolone). These data were previously summarized in Exhibit 1, filed with the Reply to Office Action on April 10, 2008 (copy enclosed), which clearly showed that the combination of an SSRI and a corticosteroid results in an effect that is greater than the sum of the effects of the SSRI and corticosteroid when administered alone.

The specification also provides data showing that several combinations of an SSRI and a non-steroidal calcineurin inhibitor mediate a synergistic decrease in proinflammatory cytokine secretion/production: effect of sertraline and cyclosporine A on IL-2 secretion/production (Table 25, page 88; 8 μM sertraline + 0.016 μM cyclosporine A); effect of sertraline and cyclosporine A on IFNγ secretion/production (Table 26, page 89; 2 μM sertraline + 0.031 μM cyclosporine A); effect of sertraline and cyclosporine A on TNFα secretion/production (Table 27, page 90; 2 μM sertraline + 0.015 μM cyclosporine A); effect of fluoxetine and cyclosporine A on IL-2 secretion/production (Table 28, page 90; 2.6 μM fluoxetine + 0.015 μM cyclosporine A); effect of fluvoxamine and tacrolimus on IL-2 secretion/production (Table 29, page 91; 5 μM fluvoxamine + 0.0031 μM tacrolimus); and effect of paroxetine and cyclosporine A on IL-2 secretion/production (Table 30, page 92; 4.4 μM paroxetine + 0.031 μM cyclosporine A). These data are also summarized in the enclosed Exhibit A, where it is clearly shown that the combination of an SSRI and a non-steroidal calcineurin inhibitor results in an effect that is greater than the sum of the effects of the SSRI and non-steroidal calcineurin inhibitor when administered alone.

Standard of Nonobviousness in View of Unexpected Result

Applicants note that the Supreme Court's recent comments on *United States v. Adams* (383 U.S. 39 (1966)) in *KSR International Co. v. Teleflex Inc.* (550 U.S. 398, 82 USPQ2d 1385 (2007), page 13) support a finding of nonobviousness in view of an unexpected result:

> The fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that Adams's design was *not obvious* to those skilled in the art. (emphasis added).

The USPTO's Examination Guidelines for Determining Obviousness Under 35 103 In View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* (Federal Register Vol. 72, No. 195, page 57534) also supports a finding of nonobviousness in view of an unexpected result:

> [I]n the case of a claim to a combination, applicants may submit evidence or argument to demonstrate that:
> (1) one of ordinary skill in the art could not have combined the claimed elements by known methods (e.g., due to technological difficulties);
> (2) the elements in combination do not merely perform the function that each element performs separately; or
> (3) the results of the claimed combination were *unexpected.* (emphasis added).

As the amended claims are directed to an unexpected synergistic effect of the combination of a corticosteroid and a SSRI, and the combination of a SSRI and a non-steroidal calcineurin inhibitor, and none of the cited prior art documents teach these synergistic effects (further described below), the obviousness rejections should be withdrawn.

None of the Prior Art Documents Teach the Claimed Synergistic Effects

Siegel is the only prior art reference, cited by the Office, that teaches the claimed combination of a corticosteroid and a SSRI. Siegel describes administering 800 combinations of 32 different immunosuppressive agents (12 disease modifying anti-rheumatic drugs (DMARDs); four glucocorticoids; and 16 non-steroidal anti-inflammatory drugs (NSAIDS)) and 25 different antidepressants. The combinations described in Siegel include 12 combinations of four glucocorticoids (dexamethasone, methylprednisolone, prednisolone, and prednisone) and three SSRIs (fluoxetine,

paroxetine, and sertraline): a subset which represents only 1.5% of the total combinations of an immunosuppressive agent and an antidepressant described in Siegel.

Siegel does not describe or suggest that the combinations of an immunosuppressive agent and an antidepressant mediate a decrease in proinflammatory cytokine secretion/production, much less describe or suggest that the combination of a corticosteroid and a SSRI would mediate a synergistic decrease in proinflammatory cytokine secretion/production. Applicants further submit that the majority of the combinations of an immunosuppressive agent and an antidepresssant described in Siegel are considerably less synergistic than the presently claimed glucocorticoid/SSRI combinations (see, Declaration of Dr. Grant Zimmermann).

Applicants have tested a majority of the combinations of an immunosuppressive agent and an antidepressant described in Siegel using an *in vitro* TNFα secretion/production assay. Using this assay, Applicants have shown that several different combinations of a glucocorticoid and an SSRI act synergistically to suppress the secretion/production of TNFα. For example, the data for the combination of prednisolone and paroxetine indicate a synergistic decrease in the secretion/production of TNFα (Exhibit 1). Using the same assay, Applicants have found that the majority of the 800 combinations of an immunosuppressive agent and an antidepressant disclosed in Siegel demonstrate no activity or synergy. For example, the agent theobromine has no effect on TNFα secretion/production when administered alone, and has no combination effect with prednisolone (Exhibit 2).

Applicants further have discovered that synergy between a glucocorticoid and a secondary agent is a rare event. Applicants have tested 858 combinations of a glucocorticoid and a secondary agent in the TNFα assay described above. These data

were assigned a synergy score: a numerical score of the observed synergy, with a higher number representing a greater observed synergistic effect for the tested combination of agents.

The majority of the tested combinations (Exhibit 3; "Historical GC-Combos") showed no synergy above that observed for "the drug with itself" (Exhibit 3; "Self-Crosses"). The glucocorticoid combinations disclosed by Siegel, exclusive of the combinations with SSRIs (Exhibit 3; "Siegel Excl Act SSRI"), show only a subtle difference from the "drug with itself" pairings, and are considerably less synergistic than the glucocorticoid/SSRI combinations (Exhibit 3; "GC Act SSRI Combos"). As only 12 combinations, or 1.5% of the total 800 different combinations of an immunosuppressive agent and an antidepresssant described in Siegel are directed to glucocorticoid/SSRI combinations, one would not reasonably predict a synergistic effect for all the combinations of an immunosuppressive agent and an antidepresssant described in Siegel.

As none of the cited art references describe or would lead a skilled artisan to expect the synergistic effect of the combination of an SSRI and a corticosteroid or the combination of an SSRI and a non-steroidal calcineurin inhibitor on decreasing proinflammatory cytokine secretion/production, and the pending claims are directed to these unexpected, synergistic effects, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicants submit that the application is in condition for allowance, and such action is hereby requested.

Transmitted herewith is a Petition to extend the period for replying to the Office Action for three months, to and including March 4, 2009, and payment of the required extension fee. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Exhibit 1

Support in Specification	SSRI	SSRI Dose	Corticosteroid	Corticosteroid Dose	% Decrease SSRI Alone	% Decrease Corticosteroid Alone	Expected % Decrease of Combination	Actual % Decrease of Combination
Table 15	paroxetine	0.375 μM	prednisolone	0.025 μM	1.4	16.5	17.9	**22.4**
Table 16	fluoxetine	7.23 μM	prednisolone	0.006 μM	29.6	7.0	36.6	**42.4**
Table 17	fluoxetine	0.009 μM	budesonide	0.009 μM	7.9	5.3	13.2	**43.6**
Table 18	paroxetine	3.0 μM	dexamethasone	0.0063 μM	9.9	26.7	36.6	**42.0**
Table 19	fluoxetine	0.036 μM	dexamethasone	0.0024 μM	22.7	0.25	23.0	**35.0**
Table 20	fluoxetine	1.80 μM	prednisolone	0.0160 μM	5.5	10.5	16.0	**19.4**
Table 21	paroxetine	3.30 μM	prednisolone	0.016 μM	29.1	12.9	42.0	**50.3**
Table 22	sertraline	4.0 μM	prednisolone	0.0160 μM	19.4	6.3	25.7	**29.0**

Exhibit A

Support in Specification and Proinflammatory Cytokine Measured	SSRI .	SSRI Dose	Non-Steroidal Calcineurin Inhibitor	Non-Steroidal Calcineurin Inhibitor Dose	% Decrease SSRI Alone	% Decrease Non-Steroidal Calcineurin Inhibitor Alone	Expected % Decrease of Combination	Actual % Decrease of Combination
Table 25 IL-2	sertraline	8 μM	cyclosporine A	0.016 μM	20.8	- 1.7	19.1	**55.7**
Table 26 IFNγ	sertraline	2 μM	cyclosporine A	0.031 μM	7.7	20.1	27.8	**34.0**
Table 27 TNFα	sertraline	2 μM	cyclosporine A	0.015 μM	- 0.6	11.2	10.6	**33.1**
Table 28 IL-2	fluoxetine	2.6 μM	cyclosporine A	0.015 μM	0.6	20.2	20.8	**28.3**
Table 29 IL-2	fluvoxamine	5 μM	tacrolimus	0.0031 μM	3.6	19	22.6	**33**
Table 30 IL-2	paroxetine	4.4 μM	cyclosporine A	0.031 μM	1.9	43.9	45.8	**57.6**